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Research Article

STUDIES ON MUCOADHESIVENESS OF EDIBLE PLANTS' EXTRACTED MUCOADHESIVE POLYMERS FOR DESIGNING, DEVELOPMENT AND IN-VIVO EVALUATION OF GASTRO-RETENTIVE TABLETS

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A B S T R A C T

Natural edible herbal polymers having sufficient mucoadhesive action have been utilized as binding and coating material to develop oral mucoadhesive tablets as controlled release drug delivery systems. The study is highlighting the edible polymers extracted from vegetables and medicinally used leaves in the treatment of jaundice in rural area and their utilization in formulation development for better health care and minimization of health hazards through proper screening and evaluation in comparison to synthetic polymers. Screening and evaluation of edible polymers have been performed by different laboratory adopted techniques such as hydration capacity determining technique, mucoadhesive strength determining techniques - Wilhelmy plate method, Falling ball method, Robinson's methods and in-vivo rabbit model method. The effective edible herbal polymer having maximum mucoadhesive strength has been selected for devising of oral mucoadhesive tablets for enhanced retention period in gastrointestinal absorption site to improve the bioavailability and efficacy of drugs. Gastro-retentive tablets based on edible herbal polymers can be retained in GIT on hydration and hence can be used for drug targeting to a particular region of GIT for extended periods of time for better efficacy in health care systems.

INTRODUCTION

Oral administration of drug formulation has been preferred for patients though the administration results in poor bioavailability and rapid passing through gastrointestinal canal (Shojaei, 1998; Khanna *et al*., 1998). Natural edible herbal polymers having sufficient mucoadhesive action can be utilized as binding and coating material to develop oral mucoadhesive gastro-retentive (Rao *et al*., 2009) drug delivery systems (OMGRDDS). Edible polymers (Sahana, 2002) made OMGRDDS may provide prolong drug action through prolong absorption of drug for enhanced retention time of formulation at gastrointestinal tract (GIT) wall lining with mucus layer (Ahuja *et al*., 1997). In this study, we have collected several edible leaves which have been used medicinally in rural area in the treatment of several disorders and used as vegetable (Bottenberg *et al*., 1991), extracted polymeric material from such leaves by hot extraction using distilled water, collected extracted polymers and tested through several experiments for quality and mucoadhesive activities (Huang *et al*., 2000). Screened edible herbal polymers based formulation OMGRDDS development has been beneficial for improved long retention time and bioavailability to achieve better therapeutic effect and minimize toxicity or hazards (Rao *et al*., 2009; Asane, 2007; Ballard, 1978). The collection, extraction and screening of natural edible polymers (Sahana, 2002), based on adhesive as well as mucoadhesive strength (Longer *et al*., 1985) in comparison to established synthetic polymers have been evaluated by applying laboratory adopted techniques such as Wilhelmy plate method, Falling ball method, Robinson's method and in-vivo rabbit model method (Sahana, 2002; Sahana and Bhaduri, 2019a; Sahana and Bhaduri, 2019b). Edible herbal polymers should be sufficiently interacting for adhesion to mucus layer in GIT, compatible, non-toxic, non irritable with the mucus layers. OMGRDDS play an important role in lingering residence time of drug(s) in GIT absorption site, enhancement of bioavailability as well as therapeutic efficacy of the content drugs through controlled release at a predetermined rate without causing dose dumping (Ballard, 1978; Sahana and Bhaduri, 2019b; Tripathi *et al*., 2019). We have been utilizing the edible polymers in devising mucoadhesive tablets (Sahana, 2002; Ahuja *et al*., 1997; Bottenberg *et al*., 1991) and evaluating in-vivo the devised tablets by administering in rabbit models through X-ray analysis of retention of barium sulphate in gastrointestinal tract (Tangri *et al*., 2011; Gavin *et al*., 2009; Alur *et al*., 1999).

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MATERIALS AND METHODS: In this study, several materials and methods have been applied to test the mucoadhesiveness of the mucoadhesive agents and for design and development novel mucoadhesive oral drug delivery systems. Extracted materials from edible plants of Indian long pepper, Shoe flower, Chinese rose flower, Jute and Vine spinach leaves have been used to test adhesiveness in comparison to Veegum, Sodium carboxymethylcellusose, Hydroxy propyl methyl cellulose, Carbopol -934 and Carbopol – 940 supplied by Dey's Medical Stores (Mfg.) Ltd. Calcutta and East India Pharmaceutical Works Ltd. Calcutta as gift samples and devise mucoadhesive tablets formulations. Pathology microslides purchased locally were used in Wilhelmy plate method after coating by mucoadhesive solutions. Goat intestinal mucus solution and mucus layered goat intestinal tissues were collected, prepared and used. Simulated Gastric Fluid U. S. P. and Simulated Intestinal Fluid U. S. P. were prepared and used. Several chemicals like pepsin, sodium chloride, hydrochloric acid; pancreatin, potassium hydrogen phosphate, sodium hydroxide and barium sulphate (radio opaque) were purchased and used as such. The 1% w/v solutions of jute leaf extract, vine spinach leaf extract carbopol – 934 and carbopol – 940 were used for granulation of adhesive tablets and 3% w/v solution were used for coating of the adhesive tablets (Sahana, 2002).

General Method of Extraction of Natural Mucoadhesives

Natural materials used for this purpose were cut into small pieces, taken in a beaker and were boiled on a hot plate at controlled temperature for at least five hours. The extracted materials were filtered through a muslin and the filtrate were collected. These extracted portions were poured in thrice of its volume of acetone with constant stirring. The mucoadhesives present in the filtrate were separated from the mixture. The extracted adhesives were washed with acetone thrice. The collected mucoadhesives were dried at 52^{o}C temperature for 7-8 hours, and stored in a desicator and kept in a refrigerator until used (Sahana, 2002).

Study of Mucoadhesives Hydration

The volume of 1 gm dried mucoadhesives (natural or synthetic) powder was measured initially. Each mucoadhesives 1.0 gm was allowed to hydrate in 10 ml of distilled water at 25^{o}C in a 10 ml graduated cylinder. The volume of the swelled mucoadhesives was measured after 5 min. of adding distilled water. Difference of the volume was noted (Sahana, 2002).

Preparation of Goat Intestinal Mucus Solution

Goat intestine were collected from the market meat shops. The mucus was collected by scraping and squeezing out the intestines. Then it was diluted with double volume water and centrifuged at 1200 r.p.m. for 30 min. The upper portion of the clear supernatant liquid was decanted and middle portion was collected and stored at below –20^{o}C in refrigerator until used (Sahana, 2002).

Preparation of Simulated Gastric Fluid U.S.P. *(Nilsson et al, 1972).*

2 g. of sodium chloride was dissolved in 7 ml hydrochloric acid containing 3.2g of pepsin. Sufficient water was added to make the volume 1000 ml. This test solution had a pH of 1.2.

Preparation of Simulated Intestinal Fluid U.S.P. *(Nilsson et al, 1972).*

6.8 g of mono basic potassium phosphate was dissolved in 250 ml of distilled water and mixed well. 190 ml of 0.2N sodium hydroxide and 400 ml of distilled water were added to the solution. 10g of pancreatin was mixed with and pH was adjusted with 0.2N sodium hydroxide to a pH 6.0. Solution was diluted with distilled water to 1000 ml.

Methods Used To Measure Bioadhesive Strength

Several methods are applied to measure the bioadhesive strength of the solutions of some natural mucoadhesive agents.

In vitro methods

Wilhelmy Plate Method

In this method, a modified and properly developed balance was used. The small glass plates or slides were coated uniformly with different Natural and Synthetic mucoadhesive solutions and dried at 52^{o}C to 60^{o}C. The prepared coated plates or slides were immersed in a goat intestinal mucus solution (pH 5.5), or simulated intestinal fluid U.S.P. (pH 6.0), or simulated gastric fluid U.S.P. (pH 1.2), for 5 min, 10 min, 15 min, 20 min, and 30 min at room temperature. The force required to pull the plate or slide out of the solution was determined under constant experimental conditions. The assembly was shown in figure. The slide was hanged by the clip on one side of the balance and immersed into the solution and one container was having weight 15g hanged another side of the balance. The water was added gradually into the container upto just sufficient to plate or slide out of the solution was measured as the adhesive strength (Nagai and Konishi, 1987).

Figure 1 Instrument used in Wilhelmy Plate Method

Robinson's Method

In this method, a modified and suitably developed balance was used. Methods using tensile strength usually measure the force required to break the adhesive bond between a model membrane and the test mucoadhesives. In this modified method, the force required to separate bioadhesive sample from freshly excised goat intestinal tissue was determined using a modified tensiometer. A section of the goat intestinal tissue, having the mucus side exposed, was secured on a weighted rubber stopper placed in a beaker containing, goat intestinal mucus solution or simulated gastric fluid U.S.P. or simulated intestinal fluid U.S.P. Another section of the same

tissue was placed over a rubber stopper, again with the mucus side exposed. Then one drop of mucoadhesive solution was placed between the two mucosal tissues. The force used to detach the mucoadhesive solution adhered two sections of mucosal tissue was then recorded. The results of the study provided important information regarding the effects of charge density, hydrophobicity and experimental conditions such as pH, ionic strength, mucolytic agents, and applied pressure on bioadhesion. Experimentations were performed at room temperature. The water was poured into the container gradually upto just sufficient to detach two mucosal tissues. The volume or weight of water was measured and considered as adhesive strength of the used solution (Nagai and Konishi, 1987)

Figure 2 Instrument used in Robinson's Method

Falling Ball Method

The mucoadhesive solution coated mustard seeds were passed through goat intestinal mucus solution (pH 5.5), U.S.P. simulated intestinal fluid U.S.P. (pH 6.0) and simulated gastric fluid U.S.P. (pH 1.2) at a specific distance i.e. 10 cm. The time required to pass this specific distance for the coated seeds were noted. All experimentations were performed at room temperature. Before experimentation small variety of mustard seeds were coated with 0.75% w/v and 1.0% w/v mucoadhesive solutions in a small laboratory type coating pan. The coated seeds were swelled with water for 5 min. before the commencement of the experiment (Nagai and Konishi, 1987).

Figure 3 Instrument used in Falling Ball Method

In vivo methods

Rabbit Model

Oral mucoadhesive tablets were administered into Rabbit. The tablets of Barium sulphate were formulated using 1% w/v mucoadhesive solution as binder. Then the tablets were coated with help of 3% w/v solution of same mucoadhesive agent .After coating one tablet was administered into the rabbit orally for each mucoadhesive agent. Then X-ray photographs of gastrointestinal tract or abdomen of the rabbit were taken after specific time of interval as follows (Sahana, 2002; Sahana and Bhaduri, 2019b). X-ray plates taken for observations after tablet administration in 1, 2, 4 and 6 hours intervals.

Barium sulphate is inert material and it is not harmful and radio opaque substance. It is used only for test not as drug. It was used to observe the mucoadhesiveness of the mucoadhesive agents and the residential time of the tablet in G.I. tract of the rabbit. This experiments were performed in same animal. Otherwise results might be varied due to different gastro-intestinal motility rate of different animals.
In this study, according to the in vitro results, the best synthetic mucoadhesive agent Carbopol 940 and the best natural mucoadhesive agent Vine Spinach leaf extract were used for in vivo testing .Observation of X-ray plate showed that the tablets were adhered in G. I. T. of the rabbit for long time according to the results. Visual observations were compared for stickability strength of the mucoadhesive agents and as well as the residential time of the tablets of different used mucoadhesive agents (Sahana, 2002; Sahana and Bhaduri, 2019b).

RESULTS AND DISCUSSION

Table 1 Results on Hydration of 1 g Mucoadhesive powder in 5 mins. and pH of the 1% w/v solutions.

Sl. No.	Name of the mucoadhesive agents	pH	Initial volume (ml)	Swelled volume (ml)	Change of volume (ml)
1	Indian long pepper leaf extract	6.5-7.0	2.2	2.5	0.3
2	Shoe flower leaf extract	6.5-7.0	2.2	2.4	0.2
3	Chinese rose leaf extract	6.5-7.0	2.1	2.3	0.2
4	Jute leaf extract	6.5-7.0	2.3	2.6	0.3
5	Vine Spinach leaf extract	6.5-7.0	2.3	2.6	0.3

It has been observed in the table 1 that the mucoadhesive agents are having good swelling properties which give good results in mucoadhesion. The pH of the 1% w/v solutions of those mucoadhesive agents are approximately similar to the pH of the water that is good for drug stability.

Wilhelmy Plate Method

Table 2 Wilhelmy Plate Method (Goat Mucus solution)

1. 0.75% w/v solution of Indian long pepper leaf extract					
Sl.No.	**Contact Time**	**Weight Required (gm)**			**Avg. wt.**
	(min.)	**Trial I**	**Trial II**	**Trial III**	**Required (g)**
1	5	5.6	5.7	5.5	5.6
2	10	5.6	5.7	5.7	5.7
3	15	5.9	5.9	5.9	5.9
4	20	5.9	6.0	6.2	6.1
5	30	6.1	6.2	6.2	6.2
2. 0.75% w/v solution of Shoe flower leaf extract					
Sl.No.	**Contact Time**	**Weight Required (gm)**			**Avg. wt.**
	(min.)	**Trial I**	**Trial II**	**Trial III**	**Required (g)**
1	5	5.6	5.4	5.4	5.4

2	10	5.4	5.4	5.3	5.4
3	15	5.5	5.6	5.5	5.5
4	20	5.8	5.7	5.6	5.7
5	30	6.0	5.8	5.8	5.8

3. 0.75% w/v solution of Chinese rose leaf extract

Sl.No.	Contact Time (min.)	Weight Required (gm) Trial I	Trial II	Trial III	Avg. wt. Required (g)
1	5	4.8	4.9	4.9	4.9
2	10	5.0	5.1	5.1	5.1
3	15	5.2	5.3	5.3	5.3
4	20	5.5	5.6	5.6	5.6
5	30	6.0	5.9	5.8	5.9

4. 0.75% w/v solution of Jute leaf extract

Sl.No.	Contact Time (min.)	Weight Required (gm) Trial I	Trial II	Trial III	Avg. wt. Required (g)
1	5	5.3	5.2	5.3	5.3
2	10	5.5	5.5	5.5	5.5
3	15	5.6	5.8	5.9	5.8
4	20	5.9	6.0	6.0	6.0
5	30	6.5	6.2	6.2	6.3

5. 0.75% w/v solution of Vine Spinach leaf extract

Sl.No.	Contact Time (min.)	Weight Required (gm) Trial I	Trial II	Trial III	Avg. wt. Required (g)
1	5	5.0	4.9	4.8	4.9
2	10	5.6	5.8	5.8	5.7
3	15	6.1	6.0	6.1	6.1
4	20	6.5	6.4	6.6	6.5
5	30	6.8	6.9	6.8	6.8

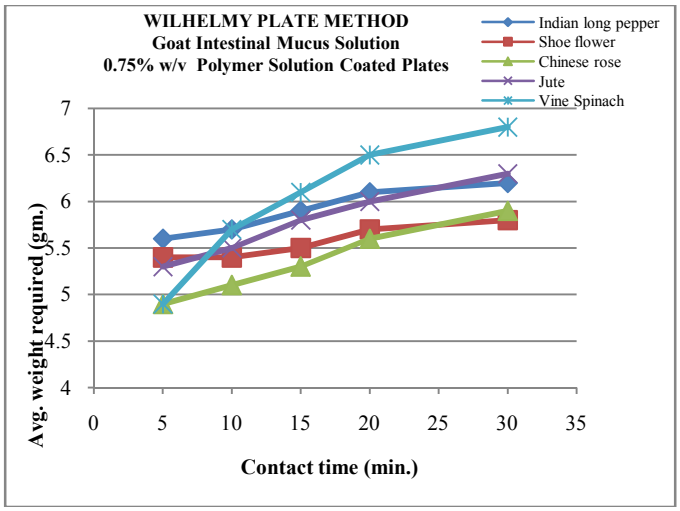

Figure 4 Graphical representation of mucoadhesive strength of polymers data from table-2.

Mucoadhesiveness of the polymers have been observed in the table 2 and figure 4 that the polymers extracted from edible leaves are having mucoadhesive strength in following order: - vine spinach > jute leaves > Indian long pepper > Chinese rose > shoe flower leaves extracted polymers. Vine spinach and jute leaves extracted polymers have been selected for formulations of mucoadhesive gastro-retentive tablet after several screening.

Table 3 Wilhelmy Plate Method (Goat Mucus solution)

1. 0.75% w/v solution of Veegum

Sl.No.	Contact Time (min.)	Weight Required (gm) Trial I	Trial II	Trial III	Avg. wt. Required (gm)
1	5	3.7	3.8	3.9	3.8
2	10	4.2	4.4	4.2	4.3
3	15	4.8	4.6	4.5	4.7
4	20	4.9	5.1	5.0	5.0
5	30	5.2	5.6	5.4	5.4

1.**0.75% w/v solution of Sodium CMC**

Sl.No.	Contact Time (min.)	Weight Required (gm) Trial I	Trial II	Trial III	Avg. wt. Required (gm)
1	5	5.3	5.3	5.0	5.2
2	10	5.5	5.4	5.4	5.4
3	15	5.6	5.6	5.6	5.6
4	20	5.7	5.8	5.7	5.7
5	30	5.8	5.8	6.0	5.9

2.**0.75% w/v solution of HPMC**

Sl.No.	Contact Time (min.)	Weight Required (gm) Trial I	Trial II	Trial III	Avg. wt. Required (gm)
1	5	5.0	4.8	5.0	5.0
2	10	5.1	5.1	5.2	5.1
3	15	5.3	5.2	5.3	5.3
4	20	5.6	5.5	5.4	5.5
5	30	5.6	5.7	5.7	5.7

3.**0.75% w/v solution of Carbapol-934**

Sl.No.	Contact Time (min.)	Weight Required (gm) Trial I	Trial II	Trial III	Avg. wt. Required (gm)
1	5	6.3	6.4	6.3	6.3
2	10	6.5	6.5	6.7	6.6
3	15	6.8	6.9	6.8	6.8
4	20	6.9	7.0	6.9	6.9
5	30	7.0	7.3	7.0	7.1

4.0.75% w/v solution of Carbapol-940

Sl.No.	Contact Time (min.)	Weight Required (gm) Trial I	Trial II	Trial III	Avg. wt. Required (gm)
1	5	6.2	6.2	6.0	6.1
2	10	6.3	6.2	6.3	6.3
3	15	6.6	6.7	6.6	6.6
4	20	6.8	6.6	6.7	6.7
5	30	7.0	6.6	6.8	6.8

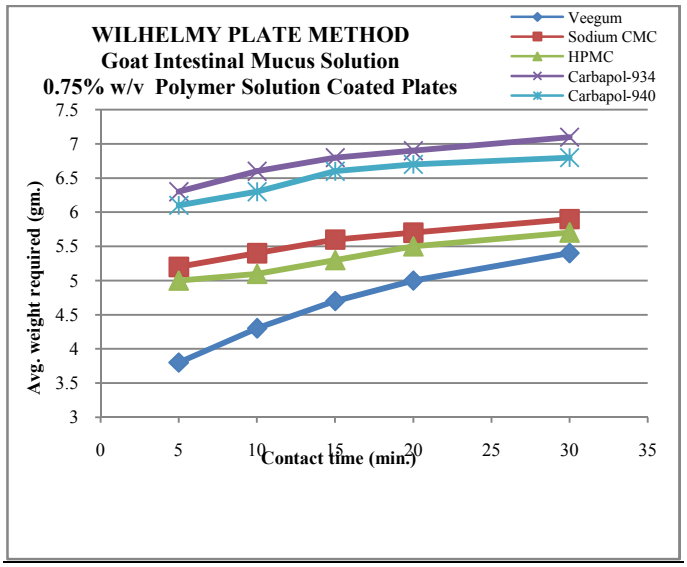

Figure 5 Graphical representation of mucoadhesive strength of polymers data from table-3.

It has been observed in the table 3 and figure 5 that the polymers are having mucoadhesive strength in following order: - Carbopol 940 > Carbopol 934 > Sodium CMC > HPMC > Veegum. Carbopol 940 and Carbopol 934 polymers have been selected for formulations of mucoadhesive gastro-retentive tablet after several screening.

Table 4 wilhelmy plate method (Simulated Gastric Fluid)

1. 0.75% w/v solution of Indian long pepper leaf extract

Sl.No.	Contact Time (min.)	Weight Required (gm) Trial I	Trial II	Trial III	Avg. wt. Required (g)
1	5	4.6	5.0	4.8	4.8
2	10	5.4	5.2	5.1	5.2
3	15	5.5	5.5	5.4	5.5
4	20	5.6	5.8	5.9	5.8
5	30	5.9	6.0	6.2	6.1

2. 0.75% w/v solution of Shoe flower leaf extract

Sl.No.	Contact Time (min.)	Weight Required (gm) Trial I	Trial II	Trial III	Avg. wt. Required (g)
1	5	4.4	4.3	4.1	4.3
2	10	4.4	4.5	4.4	4.4
3	15	4.5	4.5	4.6	4.5

4	20	4.7	4.7	4.7	4.7
5	30	4.7	4.6	4.8	4.7

3. 0.75% w/v solution of Chinese rose leaf extract

Sl.No.	Contact Time (min.)	Weight Required (gm) Trial I	Trial II	Trial III	Avg. wt. Required (g)
1	5	4.5	4.5	4.4	4.5
2	10	4.6	4.7	4.6	4.6
3	15	4.8	4.8	4.7	4.8
4	20	4.9	5.0	5.0	5.0
5	30	4.9	5.1	5.1	5.1

4. 0.75% w/v solution of Jute leaf extract

Sl.No.	Contact Time (min.)	Weight Required (gm) Trial I	Trial II	Trial III	Avg. wt. Required (g)
1	5	4.9	5.0	5.1	5.0
2	10	5.4	5.4	5.3	5.4
3	15	5.7	5.7	5.7	5.7
4	20	6.0	5.9	6.1	6.0
5	30	6.3	6.3	6.4	6.3

5. 0.75% w/v solution of Vine Spinach leaf extract

Sl.No.	Contact Time (min.)	Weight Required (gm) Trial I	Trial II	Trial III	Avg. wt. Required (g)
1	5	5.6	5.7	5.6	5.6
2	10	6.2	6.2	6.2	6.2
3	15	6.4	6.5	6.5	6.5
4	20	6.9	6.5	6.6	6.7
5	30	6.7	6.9	7.1	7.0

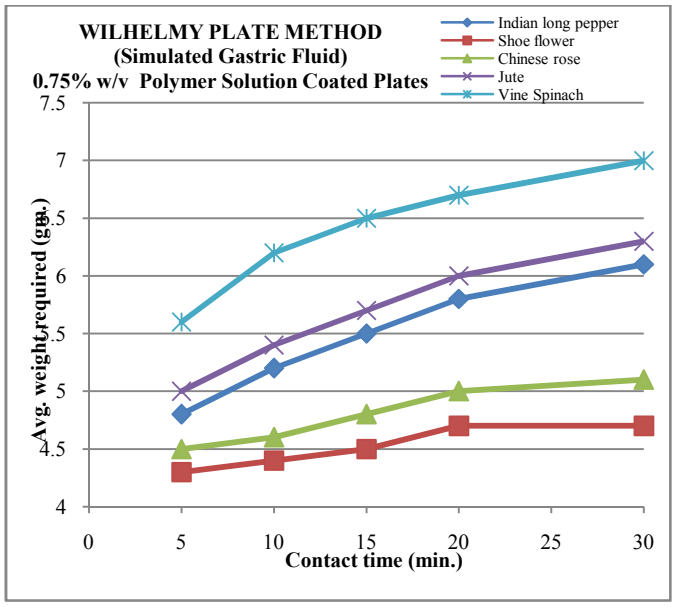

Figure 6 Graphical representation of mucoadhesive strength of polymers data from table-4.

The data in table 4 and figure 6 shows that the polymers extracted from edible leaves are having mucoadhesive strength in following order: - vine spinach > jute leaves > Indian long pepper > Chinese rose> shoe flower leaves extracted polymers. Vine spinach and jute leaves extracted polymers have been selected for formulations of mucoadhesive gastro-retentive tablet after several screening.

Table 5 Wilhelmy Plate Method (Simulated Gastric Fluid)

1.0.75% w/v solution of Veegum

Sl.No.	Contact Time (min.)	Weight Required (gm) Trial I	Trial II	Trial III	Avg. wt. Required (g)
1	5	4.1	4.1	4.0	4.1
2	10	4.2	4.3	4.3	4.3
3	15	4.4	4.5	4.6	4.5
4	20	4.8	4.8	4.7	4.8
5	30	5.1	5.0	5.1	5.1

2.0.75% w/v solution of Sodium CMC

Sl.No.	Contact Time (min.)	Weight Required (gm) Trial I	Trial II	Trial III	Avg. wt. Required (g)
1	5	3.8	3.7	3.8	3.8
2	10	4.1	4.2	4.2	4.2
3	15	4.3	4.4	4.4	4.4
4	20	4.6	4.6	4.5	4.6
5	30	4.8	4.7	4.8	4.8

3.0.75% w/v solution of HPMC

Sl.No.	Contact Time (min.)	Weight Required (gm) Trial I	Trial II	Trial III	Avg. wt. Required (g)
1	5	4.4	4.5	4.3	4.4
2	10	4.5	4.6	4.6	4.6
3	15	4.7	4.9	4.8	4.8
4	20	4.8	5.0	5.0	5.0
5	30	5.1	5.3	5.4	5.3

4.0.75% w/v solution of Carbapol-934

Sl.No.	Contact Time (min.)	Weight Required (gm) Trial I	Trial II	Trial III	Avg. wt. Required (g)
1	5	4.9	4.8	4.8	4.8
2	10	5.2	5.1	5.2	5.2
3	15	5.5	5.5	5.5	5.5
4	20	5.7	5.8	5.7	5.7
5	30	5.9	6.0	5.9	5.9

5.0.75% w/v solution of Carbapol-940

Sl.No.	Contact Time (min.)	Weight Required (gm) Trial I	Trial II	Trial III	Avg. wt. Required (g)
1	5	5.2	5.2	5.3	5.2
2	10	5.5	5.5	5.6	5.5
3	15	5.9	5.8	5.8	5.8
4	20	6.1	6.0	5.9	6.0
5	30	6.1	6.2	6.2	6.2

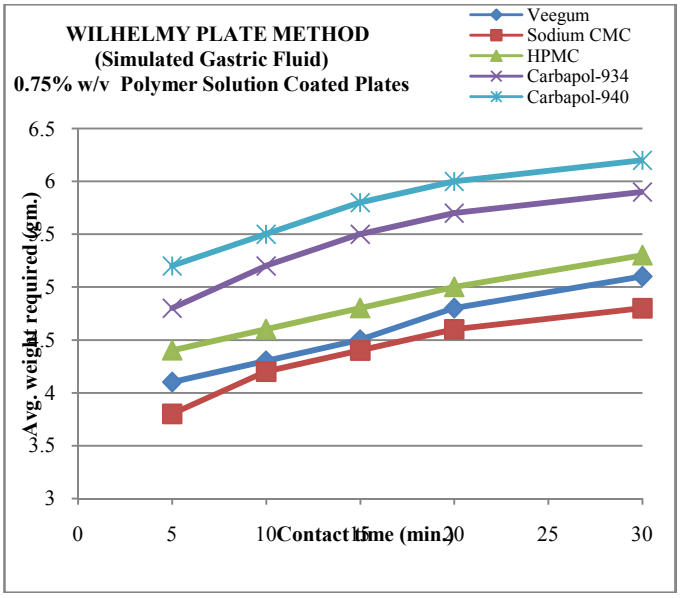

Figure 7 Graphical representation of mucoadhesive strength of polymers data from table-5.

The polymers are having mucoadhesive strength in following order: - Carbopol 940 > Carbopol 934 > HPMC > Veegum > Sodium CMC as per the data available in the table 5 and figure 7. Carbopol 940 and Carbopol 934 polymers have been selected for formulations of mucoadhesive gastro-retentive tablet after several screening.

Table 6 Wilhelmy Plate Method (Simulated Intestinal Fluid)

1. 0.75% w/v solution of Indian long pepper leaf extract

Sl.No.	Contact Time (min.)	Weight Required (gm) Trial I	Trial II	Trial III	Avg. wt. Required (g)
1	5	5.3	5.2	5.2	5.2
2	10	5.4	5.2	5.3	5.3
3	15	5.4	5.4	5.4	5.4
4	20	5.6	5.5	5.5	5.5
5	30	5.6	5.7	5.6	5.6

2. 0.75% w/v solution of Shoe flower leaf extract

Sl.No.	Contact Time (min.)	Weight Required (gm) Trial I	Trial II	Trial III	Avg. wt. Required (g)
1	5	5.1	5.2	5.3	5.2
2	10	5.8	5.6	5.5	5.6
3	15	5.7	5.8	5.8	5.8
4	20	6.0	5.9	5.9	5.9

5	30	5.8	6.1	6.2	6.0
3. 0.75% w/v solution of Chinese rose leaf extract					
Sl.No.	**Contact Time**	**Weight Required (gm)**			**Avg. wt.**
	(min.)	**Trial I**	**Trial II**	**Trial III**	**Required (g)**
1	5	5.5	5.2	5.1	5.3
2	10	5.4	5.3	5.4	5.4
3	15	5.5	5.5	5.5	5.5
4	20	5.6	5.7	5.6	5.6
5	30	5.8	5.8	5.9	5.8
4. 0.75% w/v solution of Jute leaf extract					
Sl.No.	**Contact Time**	**Weight Required (gm)**			**Avg. wt.**
	(min.)	**Trial I**	**Trial II**	**Trial III**	**Required (g)**
1	5	5.6	5.8	5.8	5.8
2	10	5.9	6.0	6.1	6.0
3	15	6.2	6.2	6.2	6.2
4	20	6.2	6.3	6.3	6.3
5	30	6.5	6.4	6.4	6.4
5. 0.75% w/v solution of Vine Spinach leaf extract					
Sl.No.	**Contact Time**	**Weight Required (gm)**			**Avg. wt.**
	(min.)	**Trial I**	**Trial II**	**Trial III**	**Required (g)**
1	5	5.6	5.7	5.6	5.6
2	10	5.9	6.0	5.9	5.9
3	15	6.1	6.2	6.2	6.2
4	20	6.3	6.4	6.4	6.4
5	30	6.5	6.5	6.5	6.5

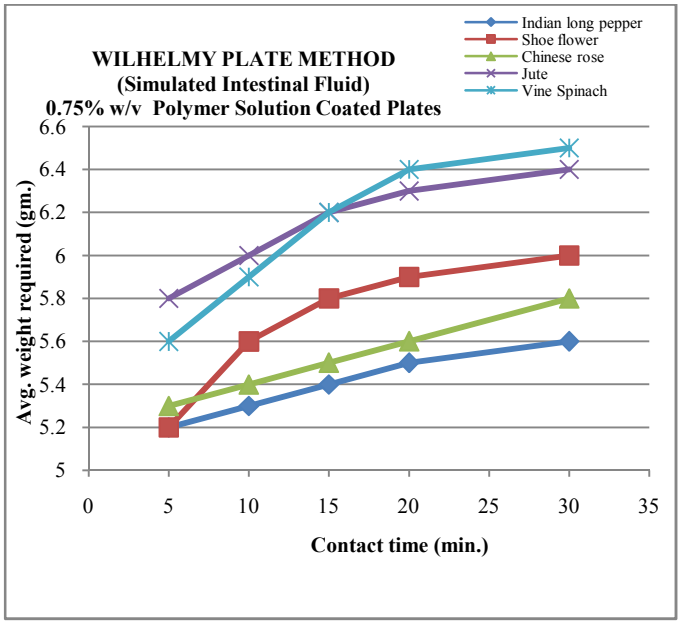

Figure 8 Graphical representation of mucoadhesive strength of polymers data from table-6.

In simulated intestinal fluid, it has been observed in the table 6 and figure 8 that the polymers extracted from edible leaves are having mucoadhesive strength in following order: - vine spinach > jute leaves > shoe flower leaves > Chinese rose > Indian long pepper extracted polymers. Vine spinach and jute leaves extracted polymers have been selected for formulations of mucoadhesive gastro-retentive tablet after several screening.

Table 7 Wilhelmy Plate Method (Simulated Intestinal Fluid)

1.0.75% w/v solution of Veegum					
Sl.No.	**Contact Time**	**Weight Required (gm)**			**Avg. wt.**
	(min.)	**Trial I**	**Trial II**	**Trial III**	**Required (g)**
1	5	4.6	4.6	4.6	4.6
2	10	5.1	5.0	4.8	5.0
3	15	5.3	5.3	5.3	5.3
4	20	5.4	5.5	5.5	5.5
5	30	5.6	5.6	5.6	5.6
2.0.75% w/v solution of Sodium CMC					
Sl.No.	**Contact Time**	**Weight Required (gm)**			**Avg. wt.**
	(min.)	**Trial I**	**Trial II**	**Trial III**	**Required (g)**
1	5	4.8	4.9	4.9	4.9
2	10	5.5	5.5	5.3	5.4
3	15	5.9	6.0	5.7	5.8
4	20	6.0	6.1	6.2	6.1
5	30	6.4	6.5	6.4	6.4
3.0.75% w/v solution of HPMC					
Sl.No.	**Contact Time**	**Weight Required (gm)**			**Avg. wt.**
	(min.)	**Trial I**	**Trial II**	**Trial III**	**Required (g)**
1	5	5.5	5.4	5.6	5.5
2	10	5.5	5.5	5.7	5.6
3	15	5.7	5.8	5.7	5.7
4	20	5.9	5.8	5.9	5.9
5	30	6.1	6.1	6.2	6.1
4.0.75% w/v solution of Carbapol-934					
Sl.No.	**Contact Time**	**Weight Required (gm)**			**Avg. wt.**
	(min.)	**Trial I**	**Trial II**	**Trial III**	**Required (g)**
1	5	6.3	6.1	6.3	6.2
2	10	6.6	6.4	6.4	6.5
3	15	6.8	6.6	6.7	6.7
4	20	6.9	6.8	6.9	6.9
5	30	6.9	7.0	7.0	7.0
5.0.75% w/v solution of Carbapol-940					
Sl.No.	**Contact Time**	**Weight Required (gm)**			**Avg. wt.**
	(min.)	**Trial I**	**Trial II**	**Trial III**	**Required (g)**
1	5	5.2	5.4	5.1	5.2
2	10	5.6	5.6	5.7	5.6
3	15	5.7	5.8	6.0	5.8
4	20	5.8	5.9	6.0	5.9
5	30	5.9	6.0	6.1	6.0

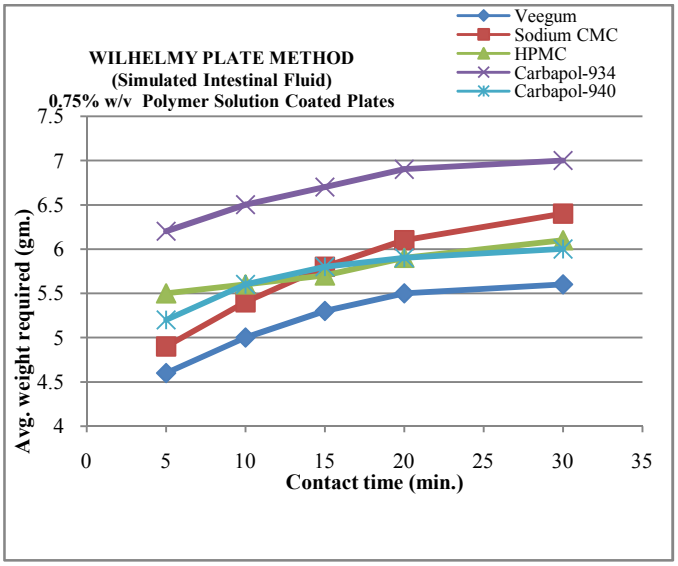

Figure 9 Graphical representation of mucoadhesive strength of polymers data from table-7.

In simulated intestinal fluid, it has been observed in the table 7 and figure 9 that the polymers are having mucoadhesive strength in following order: - Carbopol 934 > Sodium CMC > HPMC > Carbopol 940> Veegum. Carbopol 940 and Carbopol 934 polymers have been selected for formulations of mucoadhesive gastro-retentive tablet after several screening.

Falling Ball Method (Goat Intestinal Mucus solution)

1. Goat Intestinal Mucus solution
2. Uncoated and coated Mustard seeds are used as balls.
3. Natural and synthetic mucoadhesives are used as coating agents.
4. 0.75% w/v and 1.0% w/v solutions are used for coating.
5. Distance of falling – 10 cm.

Table 8 Falling Ball Method (Goat Intestinal Mucus solution)

0.75% w/v solution coated granules									
Sl. No.	**Name of the coating agents**	**Time required (seconds)**							
		Trial-1	**Trial-2**	**Trial-3**	**Trail-4**	**Trial-5**	**Trial-6**	**Trial-7**	**Avg. Time**
1.	Indian long pepper	16.0	14.0	10.5	12.0	11.5	16.0	14.5	13.50

2.	Shoe flower	12.5	15.5	12.0	16.0	10.5	10.0	14.5	13.00
3.	Chinese rose	11.5	10.0	15.5	14.5	13.5	14.0	13.5	15.14
4.	Jute	16.0	19.5	16.5	16.5	18.0	16.0	18.0	17.21
5.	Vine Spinach	18.0	22.0	19.0	19.5	15.0	15.5	17.0	18.00
6.	Veegum	15.5	16.0	20.5	13.0	17.0	14.0	13.5	15.64
7.	Sodium CMC	11.5	13.0	11.5	9.0	9.0	13.5	9.5	11.00
8.	HPMC	10.5	15.0	12.5	12.0	15.5	10.5	11.5	12.50
9.	Carbapol-934	19.5	15.0	18.0	11.5	14.5	19.5	15.5	16.14
10.	Carbapol-940	18.0	15.5	19.5	17.0	19.0	13.5	16.5	17.00

Uncoated Seeds or granules

Sl. No.	Name of the coating agents	Time required (seconds)							
		Trial-1	Trial-2	Trial-3	Trail-4	Trial-5	Trial-6	Trial-7	Avg. Time
1.	Uncoated Seeds	8.0	8.5	6.5	7.0	9.5	10.5	8.0	8.30

* 1 to 5 – Leaf extract mucoadhesive agents.

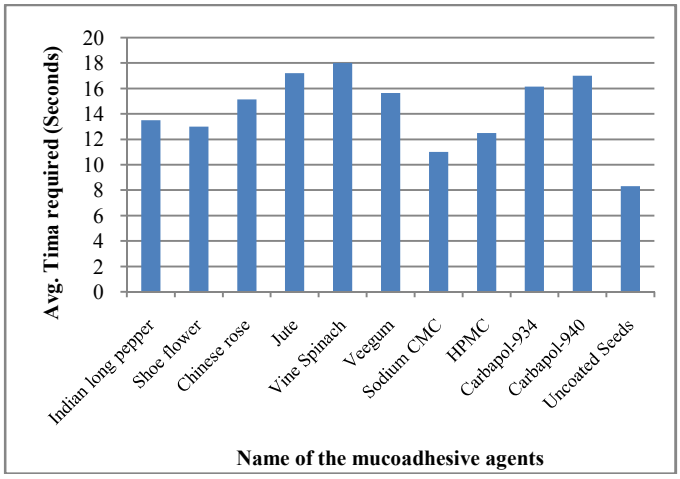

Figure 10 Graphical representation of mucoadhesive strength of polymers data from table-8.

In the falling ball method, the mucoadhesive strength of polymers have been analyzed according to the table 8 and figure 10 that the polymers extracted from edible leaves are having mucoadhesive strength in following order: - vine spinach > jute leaves > Chinese rose > Indian long pepper > shoe flower leaves extracted polymers and non-herbal polymers are having mucoadhesive strength in following order: - Carbopol 940 > Carbopol 934> Veegum>HPMC> Sodium CMC. Vine spinach and jute leaves extracted polymers, and carbopol 940 and carbopol 934 polymers have been selected for formulations of mucoadhesive gastro-retentive tablet after several screening. Vine spinach leaves extract is having greater mucoadhesive strength than carbopol 940. So herbal polymer can be used as dosage form devising agent instead of synthetic polymers.

Falling Ball Method (Simulated Gastric Fluid U.S.P.)

1. Simulated Gastric Fluid U.S.P.
2. Uncoated and coated Mustard seeds are used as balls.
3. Natural and synthetic mucoadhesives are used as coating agents.
4. 0.75% w/v and 1.0% w/v solutions are used for coating.
5. Distance of falling – 10 cm.

Table 9 falling ball method (Simulated Gastric Fluid U.S.P.)

0.75% w/v solution coated granules									
Sl. No.	**Name of the coating agents**	**Time required (seconds)**							
		Trial-1	**Trial-2**	**Trial-3**	**Trail-4**	**Trial-5**	**Trial-6**	**Trial-7**	**Avg. Time**
1.	Indian long pepper	6.1	6.0	6.5	7.2	6.8	6.5	7.4	6.6
2.	Shoe flower	5.0	4.9	4.6	4.9	6.2	4.5	5.8	5.1
3.	Chinese rose	7.9	5.2	4.7	4.4	5.6	7.8	4.6	5.7
4.	Jute	8.4	8.8	8.1	6.9	5.8	6.6	6.4	7.2
5.	Vine Spinach	5.2	6.6	8.4	8.7	9.2	8.8	9.6	8.1
6.	Veegum	4.5	5.6	5.2	6.5	6.6	5.1	5.4	5.6
7.	Sodium CMC	4.6	4.4	3.9	5.8	5.3	5.4	4.9	4.9
8.	HPMC	7.6	5.6	6.4	5.4	5.8	6.5	5.1	6.1
9.	Carbapol-934	5.6	5.9	6.7	6.3	6.5	7.6	5.8	6.3
10.	Carbapol-940	8.6	8.0	7.2	7.5	7.7	7.6	7.6	7.7
Uncoated Seeds or granules									
1.	Uncoated Seeds	4.5	3.5	6.1	4.2	4.2	3.4	3.6	4.2

* 1 to 5 – Leaf extract mucoadhesive agents.

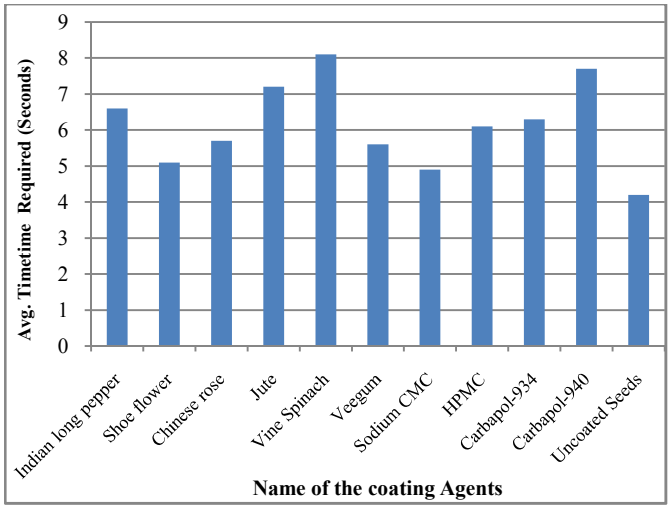

Figure 11 Graphical representation of mucoadhesive strength of polymers data from table-9.

The data given in the table 9 and figure 11 provides the information regarding mucoadhesiveness of the polymers that the polymers extracted from edible leaves are having mucoadhesive strength in following order: - vine spinach > jute leaves > Indian long pepper >Chinese rose> shoe flower leaves extracted polymers and non-herbal polymers are having mucoadhesive strength in following order: - Carbopol 940 > Carbopol 934> HPMC> Veegum>Sodium CMC. Vine spinach and jute leaves extracted polymers, and Carbopol 940 and Carbopol 934 polymers have been selected for formulations of mucoadhesive gastro-retentive tablet after several screening. Vine spinach leave extract is having greater mucoadhesive strength than carbopol-940.

Falling Ball Method (Simulated Intestinal Fluid U.S.P.)

1. Simulated Intestinal Fluid U.S.P.
2. Uncoated and coated Mustard seeds are used as balls.
3. Natural and synthetic mucoadhesives are used as coating agents.
4. 0.75% w/v and 1.0% w/v solutions are used for coating.
5. Distance of falling – 10 cm.

Table 10 Falling Ball Method (Simulated Gastric Fluid U.S.P.)

1. 1% w/v solution of Jute leaf extract

0.75% w/v solution coated granules									
Sl. No.	**Name of the coating agents**	**Time required (seconds)**							
		Trial-1	**Trial-2**	**Trial-3**	**Trail-4**	**Trial-5**	**Trial-6**	**Trial-7**	**Avg. Time**
1.	Indian long pepper	9.8	5.6	9.2	10.5	9.5	8.8	7.6	8.7
2.	Shoe flower	5.6	5.9	7.0	6.2	6.4	5.8	5.7	6.0
3.	Chinese rose	7.8	5.2	7.6	4.9	6.3	6.2	6.6	6.4
4.	Jute	7.2	8.8	7.9	9.9	10.5	11.5	10.8	9.5
5.	Vine Spinach	8.6	8.9	12.0	11.5	10.6	9.5	9.6	10.1
6.	Veegum	9.5	8.2	6.8	5.6	5.7	5.5	5.9	6.7
7.	Sodium CMC	6.2	4.1	4.6	5.0	7.4	6.1	5.4	5.6
8.	HPMC	6.0	7.8	6.5	7.0	5.6	6.4	8.5	6.8
9.	Carbapol-934	4.9	4.8	5.9	7.4	8.5	8.7	7.4	6.9
10.	Carbapol-940	12.5	12.0	9.4	7.9	7.3	7.6	9.5	9.5

Uncoated Seeds or granules

Sl. No.	Name of the coating agents	Time required (seconds)							
		Trial-1	Trial-2	Trial-3	Trail-4	Trial-5	Trial-6	Trial-7	Avg. Time
1.	Uncoated Seeds	5.4	4.2	4.5	4.1	4.9	3.7	6.2	4.7

* 1 to 5 – Leaf extract mucoadhesive agents.

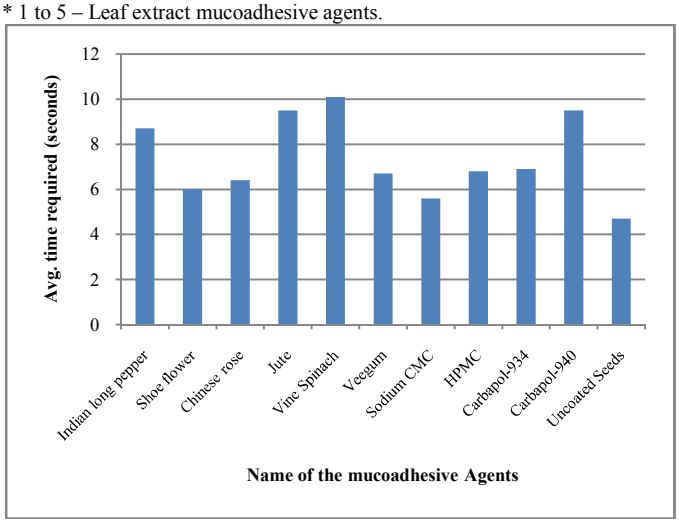

Figure 12 Graphical representation of mucoadhesive strength of polymers data from table-10.

The mucoadhesive ness has been observed as per the data given in the table 10 and figure 12 that the polymers extracted from edible leaves are having mucoadhesive strength in following order: - vine spinach > jute leaves > Indian long pepper > Chinese rose > shoe flower leaves extracted polymers and non-herbal polymers are having mucoadhesive strength in following order: - Carbopol 940 > Carbopol 934> HPMC>Veegum> Sodium CMC. Vine spinach and jute leaves extracted polymers, and Carbopol 940 and Carbopol 934 polymers have been selected for formulations of mucoadhesive gastro-retentive tablet after several screening.

Robinson's Method (Goat Intestinal Mucus Solution)

Table 11 Robinson's Method (Goat Intestinal Mucus Solution)

Sl.No.	Contact Time	Weight Required (gm)			Avg. wt.
	(min.)	Trial I	Trial II	Trial III	Required (gm)
1	5	12.5	13.5	14.0	13.33
2	10	16.0	17.0	18.5	17.17
3	15	22.5	23.5	23.5	23.17
4	20	30.0	30.5	30.0	30.17
5	30	33.5	34.5	34.5	34.16
2. 1% w/v solution of Vine Spinach leaf extract					
Sl.No.	**Contact Time**	**Weight Required (gm)**			**Avg. wt.**
	(min.)	**Trial I**	**Trial II**	**Trial III**	**Required (gm)**
1	5	18.0	17.5	19.0	18.17
2	10	19.5	20.5	22.0	20.67
3	15	23.0	25.0	27.0	25.00
4	20	30.5	31.5	32.0	31.33
5	30	40.0	38.5	35.0	37.83
3. 1% w/v solution of Carbapol-934					
Sl.No.	**Contact Time**	**Weight Required (gm)**			**Avg. wt.**
	(min.)	**Trial I**	**Trial II**	**Trial III**	**Required (gm)**
1	5	10.0	11.5	10.5	10.67
2	10	12.5	12.0	12.5	12.33
3	15	15.5	16.5	16.5	16.17
4	20	17.0	19.5	18.5	18.33
5	30	20.5	21.5	22.0	21.33
4. 1% w/v solution of Carbapol-940					
Sl.No.	**Contact Time**	**Weight Required (gm)**			**Avg. wt.**
	(min.)	**Trial I**	**Trial II**	**Trial III**	**Required (gm)**
1	5	17.5	16.0	15.0	16.17
2	10	20.5	19.5	20.5	20.17
3	15	25.0	23.5	24.0	24.17
4	20	25.5	25.0	26.5	25.67
5	30	26.5	27.0	29.0	27.50

Robinson's Method (goat intestinal mucus solution)

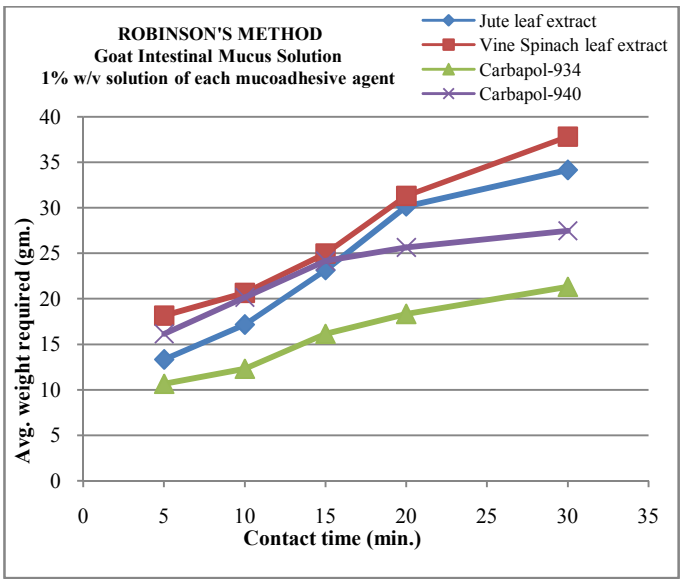

Figure 13 Graphical representation of mucoadhesive strength of polymers data from table-11.

The comparison studies among the herbal and synthetic polymers according to the data available in the table 11 and figure 13 shows that the polymers extracted from edible vine spinach and jute leaves are having greater mucoadhesive strength than the non-herbal polymers Carbopol 940 and Carbopol 934. The order of mucoadhesive strength is Vine spinach > jute > carbopol-940 > carbopol-934.

Robinson's Method (Simulated Gastric Fluid)

Table 12 Robinson's Method (Simulated Gastric Fluid)

1. 1% w/v solution of Jute leaf extract					
Sl.No.	**Contact Time**	**Weight Required (gm)**			**Avg. wt.**
	(min.)	**Trial I**	**Trial II**	**Trial III**	**Required (gm)**
1	5	12.0	11.5	10.5	11.33
2	10	13.5	13.0	13.5	13.33
3	15	15.5	15.5	15.0	15.33
4	20	18.5	19.5	18.0	18.67
5	30	21.0	21.5	21.5	21.33
2. 1% w/v solution of Vine Spinach leaf extract					
Sl.No.	**Contact Time**	**Weight Required (gm)**			**Avg. wt.**
	(min.)	**Trial I**	**Trial II**	**Trial III**	**Required (gm)**
1	5	12.0	12.5	13.0	12.50
2	10	16.5	16.0	15.5	16.00
3	15	21.0	20.5	20.5	20.67
4	20	23.5	24.0	24.0	23.83
5	30	25.5	25.5	25.5	25.50
3. 1% w/v solution of Carbapol-934					
Sl.No.	**Contact Time**	**Weight Required (gm)**			**Avg. wt.**
	(min.)	**Trial I**	**Trial II**	**Trial III**	**Required (gm)**
1	5	10.5	9.5	10.5	10.17
2	10	12.5	12.0	12.0	12.17
3	15	14.5	15.5	16.0	15.33
4	20	16.0	17.0	18.0	17.00
5	30	19.5	18.5	19.5	19.67
4. 1% w/v solution of Carbapol-940					
Sl.No.	**Contact Time**	**Weight Required (gm)**			**Avg. wt.**
	(min.)	**Trial I**	**Trial II**	**Trial III**	**Required (gm)**
1	5	10.0	11.5	11.5	11.00
2	10	14.0	13.5	12.5	13.33
3	15	15.5	16.5	16.5	16.17
4	20	18.5	19.5	20.5	19.50
5	30	23.0	22.0	21.0	22.00

Robinson's Method (Simulated Gastric Fluid)

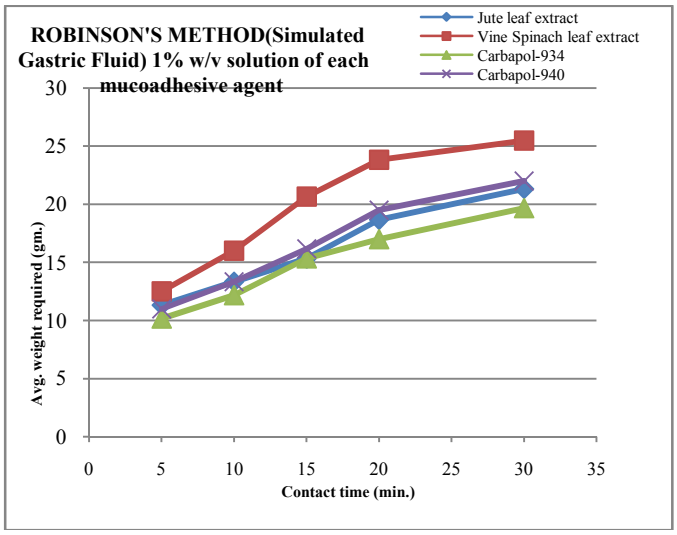

Figure 14 Graphical representation of mucoadhesive strength of polymers data from table-12.

The comparison studies among the herbal and synthetic polymers according to the data available in the table 12 and figure 14 shows that the polymers extracted from edible vine spinach and jute leaves are having good mucoadhesive strength like non-herbal polymers carbopol 940 and carbopol 934. The order of mucoadhesive strength is vine spinach > carbopol-940 > jute > carbopol-934.

Robinson's Method (Simulated Intestinal Fluid)

Table 13 Robinson's Method (Simulated Intestinal Fluid)

		1. 1% w/v solution of Jute leaf extract			
Sl.No.	Contact Time	Weight Required (gm)			Avg. wt.
	(min.)	Trial I	Trial II	Trial III	Required (gm)
1	5	10.0	11.5	10.0	10.50
2	10	12.5	13.5	12.0	12.67
3	15	15.0	15.5	15.0	15.17
4	20	17.5	18.0	17.5	17.67
5	30	20.5	21.0	19.5	20.33
		2. 1% w/v solution of Vine Spinach leaf extract			
Sl.No.	Contact Time	Weight Required (gm)			Avg. wt.
	(min.)	Trial I	Trial II	Trial III	Required (gm)
1	5	12.5	13.5	14.5	13.5
2	10	15.5	16.5	17.0	16.33
3	15	21.5	19.5	19.5	20.16
4	20	22.0	23.5	24.5	23.33
5	30	26.5	27.5	27.5	27.16
		3. 1% w/v solution of Carbapol-934			
Sl.No.	Contact Time	Weight Required (gm)			Avg. wt.
	(min.)	Trial I	Trial II	Trial III	Required (gm)
1	5	9.5	10.5	10.0	10.0
2	10	12.0	13.5	12.5	12.17
3	15	14.5	15.5	14.5	14.83
4	20	16.5	16.5	16.5	16.50
5	30	20.5	18.5	19.5	19.50
		4. 1% w/v solution of Carbapol-940			
Sl.No.	Contact Time	Weight Required (gm)			Avg. wt.
	(min.)	Trial I	Trial II	Trial III	Required (gm)
1	5	12.0	11.5	12.5	12.00
2	10	14.0	14.5	14.0	14.17
3	15	20.0	19.5	17.5	19.00
4	20	20.5	21.5	20.5	20.83
5	30	22.5	24.0	23.5	23.33

Robinson's Method (Simulated Intestinal Fluid)

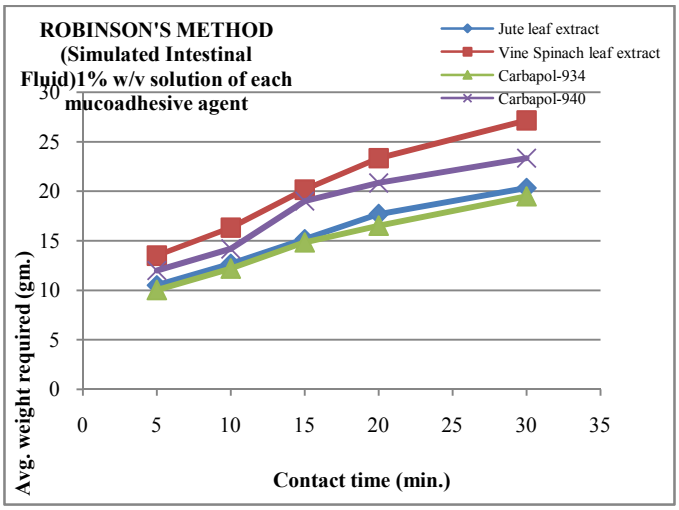

Figure 15 Graphical representation of mucoadhesive strength of polymers data from table-13.

The comparison studies among the herbal and synthetic polymers according to the data available in the table 13 and figure 15 shows that the polymers extracted from edible vine spinach and jute leaves are having good mucoadhesive strength like non-herbal polymers carbopol 940 and carbopol 934. The order of mucoadhesive strength is vine spinach > carbopol-940 > jute > carbopol-934. From this analysis the vine spinach leave extract and carbopol – 940 have been selected for mucoadhesive gastro-retentive tablet formulation devising agent for in-vivo testing in rabbit model.

RESULTS OF INVIVO METHOD

Vine spinach vegetable leaves extracted polymer and Carbopol 940 synthetic polymer made mucoadhesive tablets containing barium sulphate have been administered orally in rabbit model and taken X-ray photographs in a certain interval of 1,2,4,and 6 hours, and it has been observed in figure 16 that the main radio opaque barium sulphate tablet in the stomach remains intact up to 2 hours from administration, in 4 hours the tablet started fragmentation and moves distally in gastrointestinal canal and in 6 hours it is completely fragmented and widely dispersed in distal gut in case of vine spinach leaves extracted polymer based mucoadhesive tablets. On the other hand in case of Carbopol-940 based mucoadhesive the main radio opaque barium sulphate remains unresolved up to 4 hours from administration and in 6 hours the tablet becomes fragmented, and widely dispersed in gastrointestinal canal.

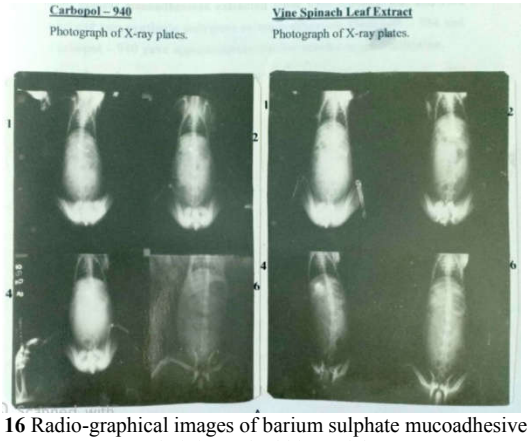

Figure 16 Radio-graphical images of barium sulphate mucoadhesive tablet administered rabbit models

In the screening of several natural and synthetic mucoadhesive agents by different methods for their mucoadhesiveness, we have obtained the mentioned results of the previous tables and figures. In comparison of the results in mucoadhesion of the mucoadhesive agents, the natural mucoadhesives jute and vine spinach leaf extracts have given the best results and those have been utilized for design and development of the oral mucoadhesive gastro-retentive tablet drug delivery systems in place of synthetic polymers for minimization of health hazards.

CONCLUSION

The advantages of herbal mucoadhesive polymers are so much attractive for developing oral mucoadhesive gastro-retentive tablet dosage form for achieving greater bioavailability and better therapeutic efficacy by lingering residence time of formulations as well as drug in absorption site. In near future herbal polymer can replace the synthetic polymers in formulation development systems and mucoadhesive gastro-retentive tablet formulation will be the potential alternative formulation for optimization of drug efficacy and minimization of toxicity in health care systems.

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